REMARKS

Claims 1-21, 23-25, 27-39, and 43-45 are pending in the application. Claims 27-39 are withdrawn as being drawn to non-elected inventions. Claims 1-21, 23-25, and 43-45 are under active consideration. Claims 7, 22, 26, and 40-42 are canceled without prejudice or disclaimer.

To expedite prosecution, claim 9 has been amended to remove the recitation "substantially all" and claim 1 has been amended to recite that at least 80% of the oil droplets in the emulsion are less than 1 micron in diameter. Support for the amendments can be found in the specification, for example, at page 18, lines 16-18. Accordingly, the specification provides adequate support for these amendments. Entry of these amendments is respectfully requested.

Claims 1 and 23 have been amended to recite that the adjuvant composition comprises an emulsion comprising submicron oil droplets and an emulsifying agent wherein the ratio of the emulsifying agent to the oil in said emulsion allows production of an emulsion wherein at least 80% of said oil droplets are less than 1 micron in diameter. Support for the amendment can be found in the specification, for example, at page 10, lines 15-20; and at page 17, line 30 through page 18, line 24. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Claim 8 has been amended to depend from claim1 instead of canceled claim 7.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Restriction Requirement

Applicants affirm the election with traverse of Group I, which corresponds to claims 1-21, 23-25, and 43-45 drawn to immunogenic and vaccine compositions, and the further election of the species of SEQ ID NO:1 (oligonucleotide) and SEQ ID NO:31 (peptide). Applicants thank the Examiner for reconsideration of the restriction requirement and regrouping of the claimed inventions.

Rejoinder

Applicants request that claims 32-39, drawn to methods of using the immunogenic and vaccine compositions of Group I, be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants request that claims 32-39 be rejoined and examined upon allowance of any of the claims drawn to the immunogenic and vaccine compositions of Group I.

Objection to the Specification

The specification is objected to on the grounds that not all of the sequences recited in the specification have a sequence identifier. Applicant has amended the specification on pages 32 and 33 to include sequence identifiers as required. Therefore, withdrawal of the objection to the specification is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 9-14 and 43-45 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 5). In particular, the Office Action alleges that "[t]he claims are vague and indefinite in the recitation of 'oil droplets substantially all of which...'" because "the metes and bounds of 'substantially all' have not been defined. Do all (*i.e.* 100%) of the oil droplets have to be less than 1 micron in diameter or can the composition have 90% of the oil droplets with a diameter of less than 1 micron?" (Office Action, page 5).

In order to expedite prosecution, claim 9 has been amended to remove the recitation "substantially all" and claim 1 has been amended to recite that at least 80% of the oil droplets in the emulsion are less than 1 micron in diameter. Support for the amendments can be found in the specification, for example, at page 18, lines 16-18. These amendments further clarify the intended subject matter of the claimed invention.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1, 3, 6, 7, 17-21, 23, and 24 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the reference of Agrawal et al. (WO 98/49288). In particular, the Office Action alleges:

> Agrawal et al. discloses a composition comprising a Neisseria antigen and a adjuvant composition comprising an oligonucleotide comprising at least one CG motif. The prior art discloses that the compositions can be used for methods for prophylactically protect [sic] a mammal from infection by a pathogen (p. 4). Agrawal et al discloses that pathogens include Neisseria spp. (p. 12). Agrawal et al discloses an oligonucleotide that has at least one CG motif and it has at least one phophorothioate bond (see p. 5; p. 10). Agrawal et al disclose that the CG motif be flanked by two purines immediately 5' to said motif and two pyrimidines immediately 3' to said motif (see p. 11). Agrawal et al disclose that the oligonucleotide would be formulated in a physiologically acceptable carrier or diluent, including without limitation saline and/or an adjuvant (pp. 8-9). (Office Action, page 7.)

In addition, claims 1-4, 6-15, 17, 23, 24, 44, and 45 have been rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by the reference of Ruelle et al. (WO 99/58683). In particular, the Office Action alleges:

> Ruelle et al. disclose a composition comprising a Neisseria antigen and a immunostimulatory oligonucleotide (abstract; p. 4; pp. 31-33). Ruelle et al. discloses that the composition may also include an adjuvant (oil-in-water emulsion, aluminum phosphate, aluminum hydroxide) (pp. 34-37). The oil-in-water emulsions comprise metabolisible [sic] oil such as squalene. Ruelle et al. discloses that the emulsion comprises 2 to 10% oil (squalene) and 0.3 to 3% Tween 80 which is an emulsifying agent (p. 37). (Office Action, page 8.)

In addition, claims 1, 3, 19-21, and 23 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the reference of Krieg et al. (WO 98/18810). In particular, the Office Action alleges:

> Krieg et al. discloses that CpG oligonucleotides are immunostimulatory and are useful as synthetic adjuvants (abstract; p. 1; claims). Krieg et al discloses that the oligonucleotides can be used to treat, prevent or ameliorate disorders that include bacterial infection (p. 10). The infectious bacteria include Neisseria gonorrhoeae and Neisseria meningitidis (p. 17). The prior art discloses that the oligonucleotide can have a phosphorothioate bond (p.

> 22)... Krieg et al discloses the claimed SEQ ID NO:1... Krieg et al discloses the use of additional adjuvants in the composition. (Office Action, pages 9-10.)

In addition, claims 1-3, 6-8, 15, 17-21, 23, and 24 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by the reference of Friede et al. (U.S. Patent No. 6,558,670). In particular, the Office Action alleges:

> Friede et al discloses a composition that comprises an antigen and an adjuvant (an immunostimulatory oligonucleotide) as well as the use of combination adjuvants (abstract; col. 3). Friede et al discloses that the immunostimulatory oligonucleotide comprises the following sequence: Purine, Purine, C,G, Pyrimidine, Pyrimidine (col. 2). Friede et al discloses that the adjuvant compositions can be used in vaccine compositions (col. 3). Friede et al discloses the claimed oligonucleotide sequence, SEQ ID NO:1 (see col. 3, 1. 55-56; sequence listing-SEQ ID NO:1). Friede et al discloses that the vaccine formulations can contain an antigen or antigenic composition capable of eliciting an immune response against a human pathogen, and that the antigen could be derived from proteins from bacterial pathogens such a Neisseria spp., *Neisseria meningitidis* and *Neisseria gonorrhoeae* (col. 5). Friede et al discloses the use of other antigens such as aluminum hydroxide, oil-in-water emulsions, aluminum salts (col. 9).

Claim 7 has been canceled; therefore, the rejections with respect to this claim are moot. Applicants respectfully traverse the rejections under 35 U.S.C. § 102 on the following grounds.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102, "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. Applicants respectfully submit that the references of Agrawal et al., Ruelle et al., and Krieg et al., do not teach all aspects of the Applicants' invention, either explicitly or implicitly.

The reference of Agrawal et al. fails to disclose immunogenic compositions comprising an emulsion comprising submicron oil droplets and an emulsifying agent as recited in independent claims 1 and 23. Nor does Agrawal et al. describe any particular second adjuvants to be used in combination with CpG oligonucleotides. Therefore, claims 1 and 23 and all claims dependent therefrom are not anticipated by Agrawal et al.

The reference of Ruelle et al. discloses immunogenic compositions comprising *Neisseria meningitidis* antigens, CpG oligonucleotides, and oil-in-water emulsions. Ruelle et al., however, fail to disclose immunogenic compositions containing emulsions comprising submicron oil droplets. Therefore, claims 1 and 23 and all claims dependent therefrom are not anticipated by Ruelle et al.

The reference of Krieg et al. discloses immunogenic compositions comprising *Neisseria meningitidis* and *gonorrhoeae* antigens and CpG oligonucleotides. Krieg et al., however, do not disclose immunogenic compositions containing emulsions comprising submicron oil droplets. Therefore, claims 1 and 23 and all claims dependent therefrom are not anticipated by Krieg et al.

The reference of Friede et al. has a priority date of April 19, 1999 and a filing date of April 29, 1999. The instant application claims priority to provisional application 60/121,792, filed February 26, 1999. Immunogenic compositions containing emulsions comprising submicron oil droplets were disclosed in provisional application 60/121,792 (see, *e.g.*, page 19, line 17 through page 20, line 17). Therefore, the claimed subject matter of the instant application is entitled to the priority date of February 26, 1999, and the reference of Friede et al. is not citable as prior art.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 2, 6-8, 15-18, and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Krieg et al. (WO 98/18810) in view of Schwartz et al. (WO 98/55495). In particular, the Office Action alleges:

> In view of the combined teachings of Krieg et al and Schwartz et al it would have been obvious to a person of ordinary skill in the art to prepare a composition that comprises a CG oligonucleotide and a Neisseria antigen and optionally another adjuvant. The prior art teaches that the Neisseria antigen can be *Neisseria meningitidis* or *Neisseria gonorrhoeae* and an adjuvant composition comprising an oligonucleotide comprising at least one CG motif. Krieg et al teaches the claimed oligonucleotide as set forth in SEQ ID NO:1 and teaches that it is a strong immune activating sequence and is a superb adjuvant. Both references teach the use of multiple adjuvants in the compositions. Schwartz et al teaches that the specifically claimed additional adjuvants can be used in the compositions to enhance the immunomodulatory activity.
> (Office Action, pages 13-14.)

In addition, claims 2-17, 25, and 43-45 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Agrawal et al. (WO 98/49288) in view of Fraser et al. (WO 99/57280). In particular, the Office Action alleges:

> In view of the combined teachings of Agrawal et al and Fraser et al it would have been obvious to a person of ordinary skill in the art to prepare a composition comprising a Neisseria antigen (*Neisseria meningitidis* serogroup B and *Neisseria gonorrhoeae*) and an adjuvant composition comprising an oligonucleotide comprising at least one CG motif. Agrawal et al teaches the claimed oligonucleotide as set forth in SEQ ID NO:1 and teaches that it has adjuvant or immunostimulating properties as well as the fact that Agrawal et al. teaches treating bacterial infections and disease. Both references teach the use of multiple adjuvants in the compositions. Fraser et al teaches the specific antigen of Neisseria claimed by Applicants set forth in SEQ ID NO:31 and teaches that all of these antigens can be used in vaccine, pharmaceutical and therapeutic compositions. (Office Action, page 15.)

Claim 7 has been canceled; therefore, the rejections with respect to this claim are moot. Applicants respectfully traverse the rejections under 35 U.S.C. § 103 on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

Applicants submit that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office, and the cited combinations are based on impermissible hindsight reconstruction.

Krieg et al. in view of Schwartz et al.

As acknowledged by the Examiner, the reference of Krieg et al. does not teach or suggest the specific recited adjuvants used in combination with CpG oligonucleotides. In particular, Krieg et al. fail to teach or suggest the use of submicron oil-in-water emulsions.

The reference of Schwartz et al. fails to cure the deficiencies of Krieg et al. Schwartz et al. describe immunogenic compositions comprising CpG oligonucleotides, antigens and additional adjuvants. However, Schwartz et al. fail to teach or suggest the use of Neisseria antigens in immunogenic compositions, nor provide any incentive for using Neisseria antigens. Furthermore, Schwartz et al. fail to teach or suggest oil-in-water emulsions, wherein at least 80% of the oil droplets are less than 1 micron in diameter. Therefore, the teachings of Schwartz et al. are not applicable to the present invention.

Thus, not all the limitations of the claims are taught or suggested by the references of Krieg et al. and Schwartz et al., considered either singly or in combination.

Agrawal et al. in view of Fraser et al.

The reference of Agrawal et al. discloses immunogenic compositions comprising *Neisseria spp* antigens and CpG oligonucleotides. However, Agrawal et al. fail to teach or suggest antigens from Neisseria species, including *Neisseria meningitidis* or *Neisseria gonorrhoeae* or any of the specific recited adjuvants used in addition to CpG oligonucleotides in immunogenic compositions. In particular, Agrawal et al. fail to teach or suggest immunogenic compositions comprising emulsions.

Fraser et al. describe immunogenic compositions comprising Neisseria antigens, including antigens from *Neisseria meningitidis* or *Neisseria gonorrhoeae* and adjuvants. However, Fraser et al. fail to teach or suggest the use of CpG oligonucleotides in immunogenic compositions, nor provide any incentive for using CpG oligonucleotides. Fraser et al. also fail to teach or suggest varying the ratio of the emulsifying agent to oil in emulsions to control the size of oil droplets (see specification, for example, at page 18, lines 7-19).

Thus, not all the limitations of the claims are taught or suggested by the references of Agrawal et al. and Fraser et al., considered either singly or in combination.

Conclusion

Thus, the references do not disclose or suggest all the limitations of the present invention, and the Examiner has not met the burden of establishing a *prima facie* case of obviousness. In the absence of some teaching or suggestion in the cited references concerning production of the precisely claimed immunogenic compositions comprising Neisseria antigens, CpG oligonucleotides, and emulsions comprising submicron oil droplets, as described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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